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1: [Control Release](#). 2002 Feb 19;79(1-3):113-22.

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FULL-TEXT ARTICLE

**Percutaneous penetration and skin metabolism of ethylsalicylate-containing agent, TU-2100: in-vitro and in-vivo evaluation in guinea pigs.**

**Sintov AC, Behar-Canetti C, Friedman Y, Tamarkin D.**

Ben Gurion University of the Negev, The Institutes for Applied Research, 84105, Beer Sheva, Israel. [asintov@bgumall.bgu.ac.il](mailto:asintov@bgumall.bgu.ac.il)

The aim of this study was to investigate the percutaneous penetration and dermal metabolism of a new potential anti-acne prodrug--TU-2100 [bis(o-carboxyphenyl ethyl ester)nonanedioate] in guinea pigs. The fluxes of this agent through excised skin after applications of TU-2100 gels at 3 and 10% concentrations were similar. However, after 24 h from the time of drug application, the total amounts of permeated TU-2100 into the skin compartment and through the skin into the receiver were 271.7 (+/-30.7 S.E.) microg/cm(2) from the 3% gel and 779.4.0 (+/-98.5 S.E.) microg/cm(2) from the 10% gel, demonstrating a relatively high skin accumulation. Higher degradation of TU-2100 to ethylsalicylate occurred after application of drug at 10% concentration than after the application of 3% gel. In contrast, the fraction of permeated drug metabolized was twofold higher after the 3% gel application than after the 10% gel ( $F(m)=20$  vs. 10.5 mole %). Since  $F(m)$  is reversibly related to the total permeating drug, the obtained values actually reflect the significant difference in TU-2100 permeation from the 3% (271.7 microg) and the 10% (779.4 microg) gels. An in vivo--in vitro comparison revealed similar drug accumulations in the skin after application of both 3 and 10% gels, however, skin metabolism was found to be significantly higher in vivo than in vitro.

PMID: 11853923 [PubMed - indexed for MEDLINE]

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## Links

### A quantitative assessment of protoporphyrin IX metabolism and phototoxicity in human skin following dose-controlled delivery of the prodrugs 5-aminolaevulinic acid and 5-aminolaevulinic acid-n-pentylester

**Gerscher S, Connelly JP, Beijersbergen Van Henegouwen GM, MacRobert AJ, Watt P, Rhodes LE.**

Dermatology Unit, Department of Medicine, University of Liverpool, Liverpool, U.K.

**BACKGROUND:** Topical 5-aminolaevulinic acid (ALA) is widely used in photodynamic therapy (PDT) to generate protoporphyrin IX (PpIX) in the skin. However, other prodrugs may be more effective. **OBJECTIVES:** The pharmacokinetics of ALA- and ALA-n-pentylester-induced PpIX, together with the phototoxicity after PDT, were compared in human skin in vivo, using iontophoresis as a quantitative drug delivery system. **METHODS:** A series of six increasing doses of equimolar prodrug solutions was iontophoresed into normal skin of the upper inner arms of 20 healthy subjects. The kinetics of PpIX metabolism in skin ( $n = 4$ ) and the response to light exposure, performed at 4.5 h ( $n = 6$ ) and 6 h ( $n = 10$ ) after application, were assessed by skin surface PpIX fluorescence and postirradiation erythema. **RESULTS:** ALA and ALA-n-pentylester showed a linear correlation between logarithm of dose and PpIX fluorescence ( $P < 0.005$ ), and logarithm of dose and skin phototoxicity with irradiation at 4.5 h ( $P < 0.001$  and  $P < 0.005$ , respectively) and 6 h ( $P < 0.05$  and  $P < 0.0001$ , respectively) after iontophoresis. Higher phototoxicity was observed with ALA-n-pentylester than with ALA when sites were irradiated at 6 h, as indicated by the significantly lower theoretical threshold dose for erythema ( $P < 0.05$ ) and the shift of the PpIX fluorescence/phototoxicity curve towards greater skin erythema at equal PpIX fluorescence levels. Depth of PpIX fluorescence in skin, as determined by fluorescence microscopy, was similar for both prodrugs, but a more homogeneous distribution of PpIX was seen with the more lipophilic ALA-n-pentylester. **CONCLUSIONS:** The observed greater phototoxicity of ALA-n-pentylester relative to ALA may be attributable to a more favourable PpIX localization in tissue and/or greater intrinsic toxicity.

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Iontophoretic delivery of ALA provides a quantitative model for ALA pharmacokinetics and PpIX phototoxicity in human skin. [J Invest Dermatol. 1997]

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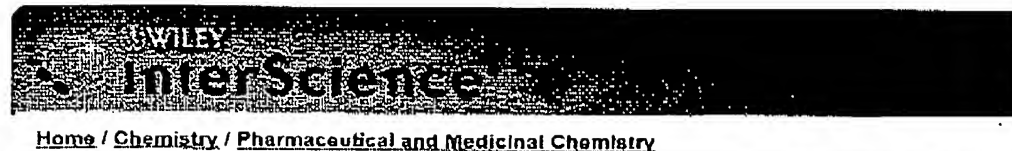
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**Designing for topical delivery: Prodrugs can make the difference**

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**Keywords**

prodrugs • diffusion cell experiments • water solubility • lipid solubility • transformed Potts-Guy equation • series/parallel equation

**Abstract**

It has been shown for homologous series of prodrugs that those members who were the more water soluble ones gave the greatest enhancement in topical delivery of the parent drug and not the more lipophilic ones. However, until recently models for topical delivery and equations to predict topical delivery focused only on lipid solubility ( $S_{LIPID}$ ) or partition coefficient ( $K_{OCT:AQ}$ ) and molecular volume (or molecular weight, MW) as parameters. Now several equations (transformed Potts-Guy or Series/Parallel) have been developed which include aqueous solubility ( $S_{AQ}$ ) as a parameter for predicting flux through skin. Experimental fluxes, solubilities, and MW from seven series of prodrugs have been fit to the transformed Potts-Guy equation to give coefficients for log solubility in isopropyl myristate ( $\log S_{IPM}$ ) and log solubility in water ( $\log S_{AQ}$ ) (0.53 and 0.47, respectively) which show, for parent drugs delivered by prodrugs from IPM *in vitro* through hairless mouse skin, that water solubility is almost as important as lipid solubility. When the transformed Potts-Guy equation was fit to data for the delivery of NSAID from mineral oil (MO) *in vivo* through human skin, the coefficients were 0.72  $\log S_{MO}$  and 0.28  $\log S_{AQ}$ . When the transformed Potts-Guy equation was fit to data for the delivery of their parent drugs by three series of prodrugs from water *in vitro* through hairless mouse skin the coefficients were 0.66  $\log S_{IPM}$  and 0.34  $\log S_{AQ}$ . Numerous recent examples are also given where more water-soluble members of homologous series of prodrugs give higher flux values from water vehicles *in vitro* through human skin than the more lipid soluble ones. © 2003 Wiley Periodicals, Inc. *Med Res Rev*, 23 No. 6, 763-793, 2003

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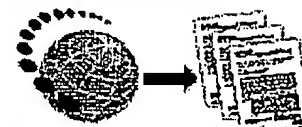
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